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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MAURICE ZAUDERER and ERNEST S. SMITH

Appeal 2009-009521[1]
Application 09/987,456
Technology Center 1600

Decided: March 29, 2010

Before TONI R. SCHEINER, DONALD E. ADAMS, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges.*

SCHEINER, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the rejection of claims 84, 88-97, 99, 103, 107-122, and 129-131, directed to a method of selecting polynucleotides which encode an antigen-specific human immunoglobulin. The claims have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Heard March 10, 2010.

STATEMENT OF THE CASE

Claims 84, 88-97, 99, 103, 107-122, and 129-131 are pending and on appeal,[2] and stand rejected under 35 U.S.C. § 103(a) as unpatentable over Rowlands,[3] Zauderer,[4] and Waterhouse.[5, 6]

The claimed invention is directed to "a method of identifying polynucleotides which encode an antigen-specific immunoglobulin molecule . . . from libraries of polynucleotides expressed in [mammalian] cells" (Spec. ¶ 25). Claim 84 is representative of the subject matter on appeal:

84. A method of selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule, comprising:

(a) introducing into a population of mammalian host cells capable of expressing said immunoglobulin molecule and permissive for vaccinia virus infectivity, a first library of polynucleotides encoding, through operable association with a transcriptional control region, a plurality of first immunoglobulin subunit polypeptides, each first immunoglobulin subunit polypeptide comprising:

(i) a first immunoglobulin constant region selected from the group consisting of a heavy chain constant region and a light chain constant region,

(ii) an immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain

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[2] Claims 85-87, 98, 100-102, and 104-106 are also pending but have been withdrawn from consideration (App. Br. 1-2). Claims 1-83 and 123-128 have been canceled.

[3] International Application WO 93/01296, published January 21, 1993.

[4] International Application WO 00/28016, published May 18, 2000.

[5] Peter Waterhouse et al., *Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires*, 21 NUCLEIC ACIDS RESEARCH 2265-2266 (1993).

[6] The two provisional rejections of the claims under the doctrine of obviousness-type double patenting set forth on pages 11-23 of the Examiner's Answer are moot, as the underlying applications have been abandoned.

variable region, wherein said variable region corresponds to said first constant region, and

(iii) a signal peptide capable of directing cell surface expression or secretion of said first immunoglobulin subunit polypeptide,

wherein said first library is constructed in a vaccinia virus vector, provided said first library is not constructed by traditional homologous recombination;

(b) introducing into said host cells a second library of polynucleotides encoding, through operable association with a transcriptional control region, a plurality of second immunoglobulin subunit polypeptides, each comprising:

(i) a second immunoglobulin constant region selected from the group consisting of a heavy chain constant region and a light chain constant region, wherein said second immunoglobulin constant region is not the same as said first immunoglobulin constant region,

(ii) an immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain variable region, wherein said variable region corresponds to said second constant region, and

(iii) a signal peptide capable of directing cell surface expression or secretion of said second immunoglobulin subunit polypeptide,

wherein said second immunoglobulin subunit polypeptide is capable of combining with said first immunoglobulin subunit polypeptide to form an immunoglobulin molecule, and wherein said second library is constructed in a vaccinia virus vector, provided said second library is not constructed by traditional homologous recombination;

(c) permitting expression of immunoglobulin molecules, from said host cells;

(d) contacting said immunoglobulin molecules with an antigen and detecting specific antigen-antibody complexes; and

(e) recovering vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunit polypeptides which, as part of an immunoglobulin molecule, are specific for said antigen.

ISSUE

The issue raised by this appeal is whether a preponderance of the evidence of record supports the Examiner's conclusion that a method of selecting polynucleotides encoding antigen-specific antibodies by introducing two vaccinia virus expression libraries - one library encoding heavy chains, the other encoding light chains - would have been obvious given the teachings of Rowlands, Zauderer, and Waterhouse.

FINDINGS OF FACT

FF1 Claim 84 is directed to a method of selecting polynucleotides encoding an antigen-specific human immunoglobulin. The method comprises co-infecting mammalian host cells with vaccinia virus vectors carrying two libraries, the first library encoding an immunoglobulin heavy chain constant region and corresponding heavy chain variable regions, the second library encoding an immunoglobulin light chain constant region and corresponding light chain variable regions;[7] expressing immunoglobulins; detecting antigen-specific immunoglobulins; and recovering vaccinia virus vectors expressing regions of interest.

FF2 Rowlands produces the humanized antibody, Campath-1H, by infecting mammalian cells with wild type vaccinia virus; co-transfecting the infected cells with transfer vectors, some encoding the light chain of Campath-1H, some encoding the heavy chain, and a selectable marker, all under the control of suitable promoters, along with sufficient vaccinia virus DNA to allow for recombination with the wild type vaccinia virus; harvesting vaccinia virus from the transfected cells; re-infecting mammalian

[7] The claim is open to either the first library or the second library to encode the heavy chain or light chain, and vice-versa.

cells with the harvested virus; selecting re-infected cells by means of the selectable marker; and harvesting recombinant virus from the selected cells. (Rowlands 5-6; Examples 4-6.)

FF3 Rowlands teaches that "a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form" (Rowlands 4).

FF4 According to Rowlands, "only a portion of the total amount of each chain which was synthesized was actually assembled. The excess heavy chain remained in the cell and the excess free light chain was mostly secreted" (Rowlands 7).

FF5 Zauderer discloses "a tri-molecular recombination method employing modified vaccinia virus vectors and related transfer plasmids that generates close to 100% recombinant vaccinia virus and, for the first time, allows efficient construction of a representative DNA library in vaccinia virus" (Zauderer 42: 25-30). Zauderer doesn't disclose an immunoglobulin library.

FF6 According to Zauderer, the tri-molecular recombination method "is a highly significant improvement over current methods for generating viral recombinants by transfection of a plasmid transfer vector into vaccinia virus infected cells . . . [which] yields viral recombinants at a frequency of the order of only 0.1%" (Zauderer 52: 9-14). In other words, Zauderer's tri-molecular recombination method introduces foreign DNA into the vaccinia virus genome much more efficiently than traditional homologous recombination, the technique used by Rowlands (Rowlands 10).

FF7 Waterhouse teaches that

> Antibody fragments, comprising paired heavy (VH) and light (VL) chain variable domains, can be displayed on the surface of filamentous bacteriophage, and rare phage (encoding antigen binding activities) selected by binding to antigen . . . The process mimics immune selection and has been used to make human antibody fragments in bacteria, without immunisation, by random combinatorial linkage . . . of diverse repertoires of VH and VL genes from lymphocytes . . . .

(Waterhouse 2265, col. 1.)

FF8 Waterhouse developed "a model system, involving the *lox*-Cre site-specific recombination system of bacteriophage P1, to lock together the heavy and light chain genes from two different replicons within an infected bacterium" so that polynucleotides encoding the heavy and light chains could be co-selected (Waterhouse 2265, col. 1).

FF9 Waterhouse demonstrated the *lox*-Cre recombination system with two vectors: an acceptor phage vector and a donor plasmid vector. The acceptor phage vector encoded the light chain fragment of a first antibody and the heavy chain fragment of an unrelated antibody, while the donor plasmid vector encoded the heavy chain fragment of the first antibody. In both vectors, the VH genes were flanked by two *loxP* sites. Eventually, following a series of recombination events, Fab fragments comprising both the light and heavy chains of the first antibody were obtained (Waterhouse 2265, col. 1).

FF10 While Waterhouse suggests that the *lox*-Cre site-specific recombination system could be used, "[i]n principle," to generate very diverse phage antibody repertoires by combinatorial infection of *E. coli* with a repertoire of heavy chains encoded on plasmids, and a repertoire of light

chains encoded by phage, the method was not actually performed using heavy and light chain repertoires. (Waterhouse 2265, col. 1-2.)

PRINCIPLES OF LAW

The Examiner has the initial burden of setting forth the basis for any rejection so as to put the patent applicant on notice of the reasons why the applicant is not entitled to a patent on the claim scope sought - this is the so-called "*prima facie* case." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). "The term '*prima facie* case' refers only to the initial examination step." *Id.* As such, the "*prima facie* case" serves as a procedural mechanism that shifts the burden of going forward to the applicant, who must produce evidence and/or argument rebutting the case of unpatentability. *Id.* "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument." *Id.*

> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should . . . carry out the claimed process; and (2) whether the prior art would also have revealed that in so . . . carrying out, those of ordinary skill would have a reasonable expectation of success.

In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991) (citation omitted).

ANALYSIS

The Examiner concluded that

> It would have been *prima facie* obvious . . . to make a library of vaccinia virus vectors as taught by Zauderer et. al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that

> their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors . . . and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al.

(Ans. 9.)

Appellants contend that the Examiner erred in concluding that one of ordinary skill in the art would have had a reasonable expectation of success in combining Rowlands with Zauderer and Waterhouse (App. Br. 12).

The Examiner's position is essentially that "one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains . . . which would encompass the heavy/light chain antibodies disclosed by Rowlands et al." (Ans. 10.)

The Examiner asserts that "it can also be 'inferred' from Waterhouse et al. that the advantages of co-selection would be just as applicable to mammalian systems as to prokaryotic systems disclosed therein because antibody selection depends on the structure of the antibody, not the source from which it was obtained" (Ans. 25). According to the Examiner, "there's no reason to expect 'less' pairing tha[n] would be formed from the use of two libraries [expressed in a prokaryotic system] because the changes made

would not affect those parts of the antibody heavy and light chain that are responsible for the pairing" (*id.* at 38-39).

Nevertheless, Appellants contend that the Examiner failed to appreciate the importance of "the fact that the Waterhouse immunoglobulin libraries are *prokaryotic* phage display libraries and the claimed invention requires two *eukaryotic* expression libraries" (App. Br. 19). Appellants contend that "the different ways in which prokaryotic and eukaryotic expression systems work" (*id.* at 13) is "at the *very heart* of why one of skill in the art would not have had a reasonable expectation of success in combining Waterhouse with Rowlands and Zauderer" (*id.* at 14-15), "as shown by the Storkus Declaration"[8] (*id.* at 14).

Dr. Walter Storkus, writing in his capacity as a member of the Scientific Advisory Board (SAB) of Vaccinex, Inc., explained that when "the idea of the present invention [was first presented] to the SAB of Vaccinex, Inc.," he was "skeptical that the present invention would succeed" (Decl. ¶6). In his Declaration, Dr. Storkus explained that he "did not think that antigen-specific antibodies could be efficiently selected from random libraries of immunoglobulin heavy and light chains expressed in eukaryotic cells *in vitro*" for several reasons, including:

> 1) the throughput for screening phage exceeded the expected throughput for screening libraries expressed in eukaryotic cells by as much as four orders of magnitude; 2) most of the work reported with antibody fragments expressed in phage was carried out with single chain Fv (scFv) in which the variable regions of immunoglobulin heavy and light chains are covalently linked, thereby increasing the likelihood that they

[8] Declaration of Dr. Walter J. Storkus, dated July 20, 2005, and submitted July 21, 2005, under the provisions of 37 C.F.R. § 1.132.

> will associate. This is significant because one of the concerns raised in the SAB was that antibodies are efficiently assembled and expressed in mature B lymphocytes because their component immunoglobulin heavy and light chains have been selected to pair properly. In contrast, we thought that random pairs of immunoglobulin heavy and light chains derived from separate libraries would be poorly matched and would, therefore, fail to associate properly in the eukaryotic cytoplasm. A related point is that antibody fragments expressed in phage, whether or not the immunoglobulin heavy and light chain variable regions are covalently linked, concentrate and are assembled in the periplasmic space. The conditions of assembly in the eukaryotic cytoplasm are far different from those that apply in the periplasmic space and it could not be known what effect this would have on antibody assembly. This difference in the conditions of assembly may explain some of the many examples of antibodies selected from phage libraries that cannot be expressed in eukaryotic cells.

(Decl. ¶ 7.)

Dr. Storkus went on to explain, at length, why his "expectations would not have changed" even in light of the Rowlands, Zauderer, and Waterhouse references (Decl. ¶ 9).

The Examiner's principal response to Appellants' arguments and Dr. Strokus' Declaration is that the "arguments (and accompanying declaration) are not commensurate in scope with the claims" because "the claims do not require 'efficient' selection, or even any 'association' at all. The light and heavy chains merely need to be 'capable' of associating" (Ans. 26-27). Even assuming this is true of the claims, it is irrelevant to the issue of whether one of skill in the art would have had a reason to do what Appellants did, given the apparent level of skepticism by those of skill in the art.

As discussed above, "patentability is determined on the totality of the record." *Oetiker*, 977 F.2d at 1445. The Examiner does not question Dr. Storkus' credentials as one of skill in this art. Dr Storkus described his expectations at the time of the invention, and provided several reasons underlying his skepticism. However, the Examiner effectively dismissed the substance of Dr. Storkus' Declaration without squarely addressing it, especially the portions dealing with the significance of the differences between prokaryotic and eukaryotic systems.

CONCLUSIONS OF LAW

The Examiner's conclusion that a method of selecting polynucleotides encoding antigen-specific antibodies by introducing two vaccinia virus expression libraries - one library encoding heavy chains, the other encoding light chains - would have been obvious given the teachings of Rowlands, Zauderer, and Waterhouse is not supported by a preponderance of the evidence.

The rejection of claims 84, 88-97, 99, 103, 107-122, and 129-131 as unpatentable over Rowlands, Zauderer, and Waterhouse is reversed.

REVERSED

cdc

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